



## Alachlor Not Estrogenic

We read with interest the article "Developmental Effects of Endocrine-Disrupting Chemicals in Wildlife and Humans," by Colborn et al. (*EHP* 101: 378-384). This paper reviews the important issue of potential long-term consequences resulting from exposure to endocrine-disrupting chemicals during early life. In this article, the authors primarily discuss agents that interfere with the functioning of endogenous estrogen. We would like to bring to your attention an important factual error in this paper. Alachlor is listed in Table 1 of that review as a chemical "reported to have reproductive and endocrine-disrupting effects." This assessment is not supported by the extensive toxicological database on alachlor and has created the incorrect impression among some readers that alachlor has estrogenic activity. Given the importance of this issue in public health, scientific, regulatory, and legislative arenas, it is necessary to clarify the scientific facts regarding alachlor and endocrine disruption.

Neither of the references cited by Colborn et al. (1,2) for alachlor discusses any data suggesting that it has estrogenic properties or interferes with reproductive activity. Both references noted that EPA concluded that minor kidney changes observed in some high-dose rats in a reproduction study were indicative of a treatment-related effect. This conclusion was contrary to that of the scientists involved in the study. Nevertheless, such changes would not represent reproductive toxicity. The EPA document (2) mentions the occurrence of adrenal tumors in high-dose female rats, but a more detailed analysis by the agency subsequently concluded that these tumors were spontaneous and not treatment related (3). The only data discussed in either reference that could be misinterpreted as a direct effect on any endocrine system is the occurrence of thyroid neoplasia in rats fed alachlor throughout their lifetime at a dose that exceeded the maximum tolerated dose (MTD). It should be noted that this dose is more than 1 million times higher than EPA's estimate of dietary human exposure (4).

The thyroid tumors in rats appear to be secondary to a hepatic effect rather than a primary effect of the chemical on the thyroid. Results from mechanistic studies have provided strong evidence indicating that chronic high-dose alachlor exposure results in increased thyroid hormone clearance via induction of hepatic uridine diphosphate

glucuronyl transferase activity, thereby causing a compensatory increase in circulating thyroid-stimulating hormone levels followed by hyperplasia and ultimately neoplasia (5). The vast body of scientific literature surrounding this general nongenotoxic mechanism has been evaluated under the auspices of EPA's Risk Assessment Forum with extensive input from the scientific and regulatory community (6); the process is threshold sensitive (i.e., there is a dose below which the thyroid disturbances and oncogenic response would not occur).

There are two classes of synthetic chemicals reported to have estrogenic activity. The first class, represented by compounds like *o,p'*-DDT, methoxychlor, and diethylstilbestrol, contain coplanar rings with chlorine, hydroxy, or methoxy substituents. The second class contains multichlorinated caged-ring structures like chlordecone. Alachlor is not structurally similar to any of these chemicals.

There is another important distinction between alachlor and several of the estrogenic compounds (e.g., DDT, PCBs, dioxins) discussed by Colborn et al. It was stated that the latter compounds have a tendency to persist in human and animal tissues, appear to sequester in all fatty tissue in the body, and have been reported in reproductive tissues. Pharmacokinetic studies in rats, mice, hamsters, and monkeys (squirrel and rhesus) have shown that the overall body clearance of alachlor is rapid (7-9). A series of autoradiography studies with alachlor and its metabolites has been conducted in rats, mice, hamsters, and monkeys (10,11). No localization in reproductive or fatty tissue was observed in any of these studies. This observation has been confirmed by direct tissue analysis.

A Federal Insecticide, Fungicide and Rodenticide Act-regulated pesticide which was recently reevaluated and found to have no toxicology data gaps (12), alachlor has been extensively investigated in a large number of studies. These include four rat and rabbit teratology studies, a three-generation rat reproduction study including gross and microscopic analyses of weanlings and adults, and several subchronic and chronic toxicity studies in rats, mice, and dogs. These studies evaluate a wide variety of endpoints that detect the effects of endocrine disruption (e.g., disturbance of fetal organ differentiation, changes in vaginal epithelium and prostate, uterotropic effects, testicular atrophy/ decreased spermatogenesis, altered mating

behavior, decreased fertility/reproductive success). The results from these numerous studies have produced no evidence of estrogenic activity. In addition, alachlor has been tested for oncogenicity in rats and mice at dose levels exceeding the MTD and did not produce tumors in mammary or other reproductive tissues cited as potential targets for estrogenic chemicals.

In summary, numerous studies have been conducted with alachlor at dose levels exceeding human and wildlife exposure by many orders of magnitude. These studies have not revealed any evidence of estrogenic effects, decreases in fertility/reproductive capacity, or tumors in reproductive tissues. It is clear that the physical and toxicological properties of alachlor are very different from the endocrine (estrogen)-disrupting chemicals, and therefore alachlor should not be classified as such.

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## Response

Heydens, Fuhremann, and Wilson wrote their letter under the assumption that in order to be an endocrine disruptor, a chemical must be estrogenic. We contend that not all endocrine disruptors are estrogenic.

The term "endocrine disruptor" was selected after many long hours of deliberation by a number of scientists (1). Certainly, any chemical that increases thyroid hormone clearance and causes a compensatory increase in circulating thyroid-stimulating hormone levels has an "unusual" effect on the endocrine system.

We tried to make this point in our article that differentiation and the life-support function of the endocrine system are, indeed, complex processes and continuously vulnerable to perturbations, either of endogenous or exogenous source. By limiting the definition of an endocrine disruptor to only estrogenicity, a host of effects on the developing and functioning endocrine system would be overlooked.

The purpose of our article was to bring to light the complexity of the endocrine system; the multiple axes of vulnerability during differentiation; the critical nature of timing of exposure to a chemical(s) that can interfere with the normal synchrony of

physiological systems not only during embryonic development, but throughout life; and the fact that vast numbers of chemicals have become a part of modern commerce that were never tested for these effects.

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